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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/826,463	04/05/2001	Nobuto Yamamoto	Y1004/20017	2419

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/826,463	YAMAMOTO, NOBUTO	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 07/11/2005 has been entered. Claims 22 and 24 are pending and being examined.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 103

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto (U. S. Patent No. 5,177,002) in view of Cooke (J Clin Invest. 1985 Dec;76(6):2420-4), Quirk (Biotechnol Appl Biochem. 1989 Jun;11(3):273-87), Lichenstein (U. S. Patent No. 5,652,352), Murphy (U. S. Patent No. 5,516,657), and Luckow (Baculovirus Expression Systems and Biopesticides, 1995 Feb:51-90).

Applicant argues that one of ordinary skill in the art would not have been motivated to combine the references' teachings and would not have had reasonable expectation of success in doing so. Applicant argues that none of the references teach how to clone GcMAF or a substantially analogous protein into a baculovirus vector. Applicant's arguments have been fully considered but they are not persuasive. Obviousness does not require absolute predictability, only a reasonable expectation of success. Applicants have not presented any evidence showing there was no reasonable expectation of success. The fact that one advantage of the Baculovirus vectors over bacterial and yeast expression vectors includes the expression of recombinant proteins that are essentially authentic and are antigenically and/or biologically active (Murphy, column 1, lines 40-52), that the list of foreign genes that may be inserted into the Baculovirus vectors includes human blood factors (Murphy, column 6, full paragraph 3), that baculovirus

vectors have become widely used to direct the expression of foreign genes (Luckow, page 51, full paragraph 1), that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (Luckow, page 74, full paragraphs 2-3), that the expression of foreign genes by baculovirus vectors is an enabling technology that permits the production of proteins that cannot often be achieved with other expression systems (Luckow, page 83, last full paragraph), and that one of ordinary skill in the art recognizes insect cells can be used for the recombinant expression of an albumin family member (Lichenstein, column 13, lines 52-55), of which the Gc protein is also a member (Cooke, Abstract; Lichenstein, column 1, lines 10-15), provides at least some degree of predictability. Hence, the argument that there is no reasonable expectation of success does not stand. Furthermore, the prior art itself reflects an appropriate level of skill in cloning foreign genes into Baculovirus vectors. Hence, one of ordinary skill in the art would be able to clone a Gc1 isoform into a baculovirus vector in the absence of any evidence to the contrary.

The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art. Obviousness does not require that an express written motivation to combine the references appear in prior art references relied upon. The fact that the Gc protein is purified from human blood (Yamamoto, column 5, full paragraph 5), that the concern about human viral contamination in products purified from blood may be avoided if these products are obtained via recombinant DNA technology (Quirk, page 273, last full paragraph), that Cooke discloses a cDNA encoding the Gc1 allele of the human vitamin D-binding protein and its nucleotide and amino acid sequence (Cooke, page 2421, Figure 2, and page 2424, left column), that Baculovirus vectors have certain advantages over bacterial and yeast expression vectors and mammalian expression systems (Murphy, column 1, lines 40-52),

that the list of foreign genes that may be inserted into the Baculovirus vectors includes human blood factors (column 6, full paragraph 3), that baculovirus vectors have become widely used to direct the expression of foreign genes (Luckow, page 51, full paragraph 1), that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (Luckow, page 74, full paragraphs 2-3), and that expression of foreign genes by baculovirus vectors is an enabling technology that permits the production of proteins that cannot often be achieved with other expression systems (Luckow, page 83, last full paragraph) would have suggested to and motivated one of ordinary skill in the art to use a baculovirus expression system to obtain the GcMAFc. Furthermore, one of ordinary skill in the art would have expected the production of GcMAFc that could not be achieved with other expression systems, as evidenced by Luckow (page 83, last full paragraph), and one of ordinary skill in the art would have expected to avoid the human viral contamination in GcMAFc purified from blood, as evidenced by Quirk (page 273, last full paragraph). For the above reasons, the prior art teaches or suggests "cloning a Gc1 isoform into a baculovirus vector." Hence, cloning GcMAF into a Baculovirus vector would have been obvious to one of ordinary skill in the art at the time the invention was made.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant's reference to *In re Vaeck* is acknowledged. Unlike the situation in Vaeck wherein expression of an antibiotic resistance-conferring "marker" gene in cyanobacteria, without more, did not render obvious the expression of unrelated genes in cyanobacteria for

unrelated proposes, the present claim is directed to or encompasses the production of a blood protein in a system that is widely used for the production of recombinant proteins that are antigenically, immunogenically, and functionally similar to their authentic counterparts (Luckow, page 51, full paragraph 1). Furthermore, the prior suggest the expression of a related blood protein (AFM) in insect cells (Lichenstein, column 13, lines 52-55). Still further, one of ordinary skill in the art would be motivated to use a baculovirus expression system because the Gc protein is purified from human blood (Yamamoto, column 5, full paragraph 5), the concern about human viral contamination in products purified from blood may be avoided if these products are obtained via recombinant DNA technology (Quirk, page 273, last full paragraph), one advantage of the Baculovirus vectors over bacterial and yeast expression vectors includes the expression of recombinant proteins that are essentially authentic and are antigenically and/or biologically active (Murphy, column 1, lines 40-52), the list of foreign genes that may be inserted into the Baculovirus vectors includes human blood factors (Murphy, column 6, full paragraph 3), baculovirus vectors have become widely used to direct the expression of foreign genes (Luckow, page 51, full paragraph 1), O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (Luckow, page 74, full paragraphs 2-3), and expression of foreign genes by baculovirus vectors is an enabling technology that permits the production of proteins that cannot often be achieved with other expression systems (Luckow, page 83, last full paragraph). The examiner concludes that *In re Vaeck* is not applicable to the present situation.

Applicant argues that the Gc protein is O-glycosylated whereas all other members of the albumin family are not, and therefore the Gc protein is unique. Applicant's arguments have been fully considered but they are not persuasive. Applicants have not presented any evidence

showing there was no reasonable expectation of success. Even if all other members of the albumin family are not O-glycosylated, this would still not rebut the teaching, suggestion, and motivation to clone a Gc isoform into a baculovirus vector, as discussed above.

Applicant argues that there is no evidence in Murphy to suggest that a sialylated protein could be generated as easily in a baculovirus vector as a non-sialylated one. Applicant's arguments have been fully considered but they are not persuasive. Applicants have not presented any evidence showing there was no reasonable expectation of success. In fact, Luckow discloses that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (page 74, full paragraphs 2-3), which suggest that a sialylated protein could be generated as easily as a non-sialylated one in a baculovirus vector.

New Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 112

Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation in step (c) of claim 24 lacks description in the originally filed disclosure, which raises the issue of new matter and violation of the provisions of the first paragraph of 35 U.S.C. 112.

Applicant argues that although a protein sequencing protocol is not disclosed, one of ordinary skill in the art would know how to perform this procedure. Applicant argues that the

amino acid sequence of wild-type Gc protein is disclosed and that one would be able to compare the sequence of the cloned protein with the disclosed sequence. Applicant's arguments have been fully considered but they are not persuasive. Although one of ordinary skill in the art may know how to perform the procedure in step (c), the original specification cannot be said to fairly describe or suggest the concept of the procedure in step (c). At best it might be obvious to the skilled artisan that it would be desirable to perform the procedure in step (c). However, the written description does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. It extends only to that which is disclosed. Since the limitation in step (c) did not appear in the specification as filed, it introduces a new concept and violates the description requirement of 35 U.S.C. § 112, first paragraph.

Claim Rejections - 35 USC § 103

Claims 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto (U. S. Patent No. 5,177,002) in view of Cooke (J Clin Invest. 1985 Dec;76(6):2420-4), Quirk (Biotechnol Appl Biochem. 1989 Jun;11(3):273-87), Lichenstein (U. S. Patent No. 5,652,352), Murphy (U. S. Patent No. 5,516,657), and Luckow (Baculovirus Expression Systems and Biopesticides, 1995 Feb:51-90) as applied to claim 22 above, and further in view of Lu (Protein Expr Purif. 1993 Oct;4(5):465-72).

Yamamoto in view of Cooke, Quirk, Lichenstein, Murphy, and Luckow teach a process for producing GcMAFc comprising cloning a Gc1 isoform into a baculovirus vector, expressing the cloned Gc1 isoform, contacting the expressed Gc1 isoform with immobilized β-galactosidase

and sialidase, and obtaining the GcMAFc, as discussed above. Yamamoto in view of Cooke, Quirk, Lichenstein, Murphy, and Luckow do not teach sequencing the cloned Gc1 peptide.

Lu teaches that the potential mistranslation that may happen in the production of any recombinant protein should seriously be taken into consideration. Appropriate purification processes should be evaluated and implemented to eliminate the undesired minor variant forms. A combination of protein analytical techniques, as described, can ensure the quality of the final product. See page 471, right column, full paragraph 1. Lu describes the analytical technique of protein sequencing (Abstract; page 467, left column, full paragraph 3). Lu does not teach a process for producing GcMAFc comprising cloning a Gc1 isoform into a baculovirus vector, expressing the cloned Gc1 isoform, contacting the expressed Gc1 isoform with immobilized β-galactosidase and sialidase, and obtaining the GcMAFc.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to clone a Gc1 isoform into a baculovirus vector, express the cloned Gc1 isoform, contact the expressed Gc1 isoform with immobilized β-galactosidase and sialidase, and obtain the GcMAFc, as taught by Yamamoto in view of Cooke, Quirk, Lichenstein, Murphy, and Luckow, and to modify that teaching by sequencing the cloned Gc1 peptide, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification to ensure the quality of the final GcMAFc product. The invention is prima facie obvious over the prior art.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
SEPTEMBER 16, 2005